Schnitzler syndrome is a rare disease presenting with chronic urticaria and monoclonal gammopathy. Its pathogenesis is unclear and therapies effective in chronic urticaria remained without effect (1, 2). However, whether systemic or cutaneous IL-1 elicits urticaria in these patients is not known, because the source of IL-1 remained enigmatic. Here we demonstrate for the first time the presence of active IL-1β by immunohistochemistry in dermal cells of affected skin in a patient with Schnitzler syndrome. This not only underlines the rationale to treat Schnitzler syndrome with IL-1 blocking agents; it also demonstrates that immunoglobulin M (IgM), or yet unknown factors associated with monoclonal gammopathy in these patients, trigger IL-1 activation also in the skin, as gene defects do in patients with Muckle-Wells (MWS) or cryopyrin-associated periodic syndromes (CAPS) (3, 4). Consequently, treatment with the IL-1 receptor antagonist (IL-1RA) anakinra, initiated as first-line monotherapy, led to complete remission of symptoms within 2 days, and long-lasting remission for more than 3 years was achieved by daily administration of anakinra.

CASE REPORT

A 59-year-old woman presented with a 5-year-history of daily episodes of urticaria. Wheals were located at the trunk, the upper limbs and the thighs and were accompanied by musculoskeletal and bone pain as well as by attacks of fever. In contrast to patients with chronic urticaria, wheals never elicited itch, and therapies with high-dose antihistamines had no effect. Upon physical examination generalized urticaria was documented (Fig. 1A). Histological analysis of wheals revealed a sparse infiltrate of neutrophils devoid of leukocytoclasis compatible with the diagnosis urticaria without signs of vasculitis (Fig. 1B). Importantly, immunohistochemistry performed from specimens of affected skin revealed dermal expression of active IL-1β, as shown by staining with a monoclonal antibody recognizing cleaved IL-1β (Fig. 1C), whereas cleaved IL-1β was absent in control skin (not shown). Laboratory investigations showed leukocytosis (10.94 × 10^9/l), elevated erythrocyte sedimentation rate of 53 mm/h and increased C-reactive protein (CRP) (57.5 mg/l). Increased IgM levels (516 mg/l) were detected, while serum levels for IgG and IgA were normal. In addition, elevated levels of free kappa light chains (51.1 mg/l) were detected and immunofixation confirmed a monoclonal gammopathy of the IgM type. No lymphoproliferative disorder could be detected in the bone marrow biopsy. Ultrasound revealed a mild splenomegaly without hepatomegaly and peripheral lymphadenopathy. Arthritis was ruled out by 3-phase-scintigraphy.

Based on the clinical and laboratory findings, the diagnosis of Schnitzler syndrome was made. Given the observed IL-1β expression in affected skin lesions, and recent reports on patients with Schnitzler syndrome that failed to respond to any other treatment but the use of the IL-1RA anakinra, prompted us to administer anakinra as first-line therapy. Subcutaneous injection of 100 mg anakinra per day was started, and within 48 h a complete and sustained remission of the urticarial rash occurred (Fig. 2A), while the patient noticed the disappearance of musculoskeletal pain and arthralgias. Leukocyte counts rapidly normalized, and elevated C-reactive protein levels constantly decreased within the first 3 days after onset of therapy (Fig. 2B). Monotherapy with anakinra 100 mg daily was continued in the absence of any side-effects for more than 3 years, and the patient is still in complete remission.

DISCUSSION

Schnitzler syndrome typically presents with non-itching urticaria that is unresponsive to even high-dose antihistamines. The diagnosis of Schnitzler syndrome can be considered on the basis of the 2 major criteria: “chronic urticarial rash” and “monoclonal gammopathy” in combination with at least 2 minor criteria as reviewed by Lipsker et al. (1) and de Koning et al. (2). Exclusion of haematological malignant diseases and other autoimmune disorders is mandatory.
The pathogenesis of the symptoms in Schnitzler syndrome is still unknown. Interestingly, excessive secretion of IL-1, IL-6 and tumour necrosis factor (TNF) after lipopolysaccharide stimulation of peripheral blood mononuclear cells from patients with Schnitzler syndrome has been demonstrated, and only administration of a caspase inhibitor reduced IL-1 secretion, while blocking TNFα had no effect (5). Together with our new findings of dermal expression of active IL-1β this points to a central role of the inflammasome-controlled IL-1 production as a crucial step in its pathophysiology. The best evidence that Schnitzler syndrome is a disease of exaggerated IL-1 activation is also found in the skin (8, 9). Detection of cleaved IL-1β in the skin may help to distinguish urticaria in Schnitzler syndrome from other forms of urticaria, as we could not detect IL-1β in specimens from patients with chronic idiopathic urticaria (data not shown). Clinical improvement was accompanied by declining leucocyte counts and CRP levels within a few days demonstrating the systemic effects of IL-1R blockade. Full remission lasting for more than 3 years was achieved by continuous therapy with daily subcutaneous injections. To our knowledge this is also the first report demonstrating such long-lasting improvement of Schnitzler syndrome by monotherapy with anakinra in the absence of any side-effects.

Although Schnitzler syndrome has a benign course, development of Waldenström’s macroglobulinaemia has been reported (2). Thus, long-term follow-up is necessary to detect development of haematological malignancies. Whether therapy with anakinra or newly developed IL-1 blocking drugs (Rilonacept or Canakinumab) may decrease the risk of developing haematological malignancies due to an ongoing inflammatory immune response has to be evaluated. Taken together, administration of the IL-1RA anakinra has emerged as an effective treatment for the still enigmatic Schnitzler syndrome and should be the therapy of choice in newly diagnosed patients.

REFERENCES